Modern Concepts of Cardiovascular Disease

Published monthly by the AMERICAN HEART ASSOCIATION

1775 BROADWAY, NEW YORK 19, N. Y.

VOL. XX APRIL, 1951 No. 4

CURRENT VIEWS ON THE RELATION OF CHOLESTEROL METABOLISM TO DEGENERATIVE ARTERIAL DISEASE

Clinical and experimental research in the field of atherosclerosis during the past decade has given increasing impetus to the idea that the disease is etiologically linked to cholesterol metabolism. Scientific, as well as popular literature at the present time is replete with spectacular, although still fragmentary, data implicating the serum cholesterol in the genesis of atheromatous arterial changes.

There is general agreement that the disease begins as fatty deposits in the root, arch, and posterior wall of the aorta, especially at the origin of the intercostal arteries. The fatty material stimulates growth of fibrous tissue and atheromas result from softening of the centers of the lesions to give masses of soft lipid material. Thrombosis is favored both by injury to the vessel wall opposite the lesions and obstruction to blood flow. The fatty material may, itself, accelerate blood clotting processes.

Theories too numerous to mention have been proposed to explain the presence of this fatty material. At the present time, the most widely accepted view is that it is derived from the blood, since the simple fatty deposits of atherosclerosis have the same lipid composition as the blood plasma and the normal intima. Present-day research is concerned primarily with the reasons for its precipitation from the blood of some individuals and not of others.

Certain factors have long been known to be associated with the premature appearance of atherosclerosis. These may be subdivided into mechanical, metabolic and endocrine, and hereditary factors.

Mechanical factors include increased blood pressure and the tendency for atheromata to form at points of stress in the vascular tree. Increased incidence in diabetes mellitus, myxedema, lipoid nephrosis, xanthomatosis, and obesity, and the differential sex ratio in coronary artery disease, are probably the result of metabolic and endocrine factors.

The tendency for the disease to occur at younger ages in successive generations suggests that heredity plays a role. We have observed a family where the original patient suffered a coronary thrombosis in the sixties, his son had one at age 45, and his grandson at age 28. Most practicing physicians have seen similar, if not such extreme, examples of familial incidence of the disease.

The importance of increased blood pressure is well established and is thought to hasten the process by constant, greater-than-normal trauma to the intima. The tendency for atheromas to form at points of stress, such as the origins of the intercostal and coronary arteries, is likewise thought to be related to greater trauma to the intima at these points. Hueper[1], however, stresses the fact that eddies and currents are necessarily greater at anatomical points of stress, and any instability of the plasma colloids, including cholesterol and its esters, would tend to lead to their precipitation at such points.

Mechanical factors cannot be regarded as primary, since atheromas do not form in all individuals at points of stress, and the disease occurs with fair frequency in individuals with normal blood pressure.

The metabolic and endocrine factors mentioned—with the exception of sex incidence and obesity—are known to be associated with abnormalities of the serum lipids, particularly an increase in serum cholesterol. Whether heredity operates through anatomical factors, slight aberrations in endocrine and metabolic function or through the family cookbook—or through complex mixtures of the three—has not been established.

Pathology, animal experiments, and many comparative studies of serum lipids in normals and patients support the idea that some abnormality of the serum lipids is the primary factor in the development of atherosclerosis. The evidence of pathology—that extensive, premature atherosclerosis is found associated with diseases in which the serum lipids are known to be grossly abnormal, such as diabetes mellitus, myxedema, lipoid nephrosis, and xanthomatosis—is well known.

So far as animal experiments are concerned, lesions resembling those of atherosclerosis have now been produced in rabbits, guinea pigs, mice, dogs, chickens, and geese by cholesterol, or cholesterol, fat, and thiouracil feeding; in the case of geese, force-feeding of normal rations low in fat and cholesterol resulted in atheromatous lesions.

Earlier reports of failure to produce atherosclerosis in certain species have been followed by success when longer experiments or accessory means of obtaining significant hypercholesterolemia have been employed. Prolonged serum cholesterol levels above the normal, then, will be followed by the development of vascular lesions in most species.

Many attempts have been made to prove or disprove the existence of a relation between the cholesterol content of the blood and the development of atherosclerosis in humans by comparing the cholesterol content of the blood with the condition of the arteries at autopsy. Hueper[1] points out that results are naturally contradictory, since atherosclerosis is a disease which takes years to develop and may persist for years after cessation of action of the causal agent.

It is of interest that many studies reporting no increase in serum cholesterol in atherosclerosis have been of the above kind; or atherosclerosis has erroneously been assumed to exist because of the presence of hypertension or palpable hardening of radial or dorsalis pedis arteries.

An increasing number of studies of serum cholesterol in patients with coronary atherosclerosis, as evidenced by myocardial infarction or typical angina pectoris, report a definite tendency of hypercholesterolemia in patients so studied. Another important fact established by such studies has been that marked fluctuations in serum cholesterol are common in patients with coronary artery disease but not in normals.

Recent animal experiments suggest that the actual height of the cholesterol level attained is not as important as the ratio of total cholesterol to lipid phosphorus. In experimental atherosclerosis, most species exhibit an inability to have the serum phospholipid keep pace with the rise in serum cholesterol occasioned by high cholesterol feeding. Thus, Davidson and associates[2] have shown an increase of the molar ratio of cholesterol to phospholipid of 1:1 in normal dogs to 5:1 in cholesterol-thiouracil fed dogs in which atherosclerosis has been produced.

Conversely, Kellner, Correll and Ladd[3] have shown a marked decrease in the incidence and severity of experimental atherosclerosis in cholesterol-fed rabbits given intravenous detergents, such animals exhibiting markedly elevated serum phospholipids as well as elevated cholesterol. These facts suggest that the serum phospholipids exert a stabilizing effect upon the colloid state of cholesterol in the blood, not a surprising conclusion, since lecithin, the chief phospholipid of serum, is a well-known emulsifying agent.

Very recently, Gertler and co-workers[4] have reported on an extensive series of normals and coronary artery disease patients. The cholesterol: lipid phosphorus ratio was significantly higher in patients than normals.

The most spectacular work relating serum lipids to atherosclerosis is the recent demonstration by Gofman[5] of the occurrence in high concentration of so-called "giant molecules" of cholesterol in the blood of patients with myocardial infarction. Utilizing the analytical ultra-centrifuge and a special flotation technique, Gofman has been able to separate from serum several species of lipo-protein complexes containing cholesterol. One particular group, designated the S*f* 10-20 class, appears to be related to human atherosclerosis, as evidenced by their occurrence in much higher concentration in the blood of patients who have suffered a myocardial infarction than in normals.

Their relation to atherosclerosis is further suggested by the fact that, whereas they are absent from the serum of normal rabbits, cholesterol-fed rabbits eventually develop them in high concentration. The degree of atherosclerosis at autopsy is correlated with the height of the final concentration of S*f* 10-20 molecules attained.

The concentration of S*f* 10-20 molecules bears no absolute relation to the total cholesterol level of the blood, but there is a trend towards higher S*f* 10-20 concentrations with higher total cholesterols. The possible relationship between cholesterol:lipid phosphorus ratio of serum and concentration of S*f* 10-20 molecules has not been adequately investigated.

The most encouraging aspect of this work has been the demonstration that adherence to a diet restricting cholesterol to 200 mg. or less and fat to 50 gm. or less, daily, for periods of four weeks or longer, results in consistent lowering of the concentration of these molecules.

In this connection, it is of interest that Keyes[6] has shown that an habitual intake of cholesterol of varying amounts from 250 to 800 mg. per day shows no correlation with serum cholesterol level; but when cholesterol is completely eliminated from the diet—such diets being also essentially fat-free—a regular and rapid decline in serum cholesterol level occurs. Limited additional experiments suggest that fat is just as important as cholesterol in maintaining a relatively high level of serum cholesterol.

Work of this kind suggests that previous studies which "proved" that diet did not influence cholesterol level were based on insufficient restriction of fat and cholesterol. More integrated studies of the effect of very restricted fat diets upon serum content of S*f* 10-20 molecules, cholesterol, and phospholipid may eventually reveal that some basic minimum of fat in the diet will serve to maintain these entities in serum at levels resembling those in "normals," as opposed to known atherosclerotics.

It is not easy, however, to change the habits of a lifetime, and rigid limitation of fat and cholesterol usually results in marked limitation of total calories and consequent weight loss. Since the beneficial effects of weight loss in overweight patients with vascular disease is well established, current popularization of the low fat, low cholesterol diet will probably have a totally beneficial effect; but a word of caution is in order against too rigid diets that may be inadequate in protein and other essentials, although desirably low in fat.

Information is by no means complete, but it well may be that drastic changes in food habits—beginning in the nursery—will grow out of such studies. Furthermore, if research along these lines continues its present pace, it may eventually be possible not only to pick from the general population individuals who are developing the disease, but also to institute dietary and other therapeutic measures to retard and possibly reverse the degenerative changes before the more disastrous results of these changes occur.

Mary Louise Eilert, M.D.
Chicago, Ill.

1. Hueper, W. C., Experimental Studies in Cardiovascular Pathology. XIII. Vibratory Lability of Plasma Colloids in Rabbits and Dogs following Ingestion of Cholesterol. *Arch. Path.*, 41:139: 1946.

2. Davidson, J. D., Liese, L. A., and Kendall, F. E., Serum Lipids in Experimental Canine Arteriosclerosis. *Am. Heart J.*, 38:462:1949.

3. Kellner, H., Correll, J. W., and Ladd, A. T., Modification of Experimental Atherosclerosis by Means of Intravenous Detergents. *Am. Heart J.*, 38:460:1949.

4. Gertler, M. M., Gorn, S. M., and Lerman, J., The Interrelationships of Serum Cholesterol, Cholesterol Esters and Phospholipids in Health and in Coronary Artery Disease. *Circulation*, 2:205:1950.

5. Gofman, J. W., Jones, H. B., Lindgren, F., Lynn, T. P., Eilliot, H. H., and Strisoner, B., Blood Lipids and Human Atherosclerosis. *Circulation*, 2:161:1950.

6. Keyes, A., The Relation in Man Between Cholesterol Levels in the Diet and in the Blood. *Science*, 122:79:1950.

PROGRAM
TWENTY-FOURTH SCIENTIFIC SESSIONS
AMERICAN HEART ASSOCIATION
June 8-9, 1951
Vernon Room, Haddon Hall, Atlantic City, N. J.

FIRST SESSION
9:00 A.M., Friday, June 8

Chairman: T. Duckett Jones, American Council on Rheumatic Fever

1. THE MEDICAL SUPERVISION OF THE POTENTIAL RHEUMATIC FAMILY FOR EARLY DIAGNOSIS AND TREATMENT.
   May G. Wilson and Nathan Epstein, New York, New York.
2. RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE: A TWENTY-YEAR REPORT ON 1000 PATIENTS FOLLOWED SINCE CHILDHOOD.
   Edward F. Bland and T. Duckett Jones, Boston, Massachusetts.
3. THE OCCURRENCE OF RHEUMATIC FEVER DURING THE FIRST FIVE YEARS OF LIFE: REPORT OF 23 CASES.
   R. Bruce Logue and J. Willis Hurst, Atlanta, Georgia.
4. SCHOOL CARDIAC SERVICES.
   Jacob M. Cahan, Philadelphia, Pennsylvania.
5. THE EFFECT OF ACTH AND CORTISONE ON RHEUMATIC CARDITIS: OBSERVATIONS ON 18 CASES.
   Ann G. Kuttner, Janet S. Baldwin, Currier McEwen, and Joseph J. Bunim, New York, New York.
6. THE EFFECT OF TREATMENT OF STREPTOCOCCAL DISEASE ON THE DEVELOPMENT OF ELECTROCARDIOGRAPHIC ABNORMALITIES AND RHEUMATIC FEVER.
   Edward O. Hahn, Daniel Stowens, and George C. Eckhardt, Cheyenne, Wyo. and Cleveland, Ohio.
7. "ACUTE PHASE REACTANTS" AS CRITERIA OF ACTIVITY IN RHEUMATIC FEVER.
   Vincent C. Kelley, Salt Lake City, Utah.
8. DIAGNOSTIC PROBLEMS OF RHEUMATIC FEVER AND THEIR IMPACT ON THE MANAGEMENT OF THE RHEUMATIC PATIENT.
   Frederick J. Lewy, New York, New York.
9. THE RESPONSIBILITY OF THE PHYSICIAN IN THE SELECTION OF PATIENTS FOR THE SURGICAL TREATMENT OF MITRAL STENOSIS.
   Dwight E. Harken, Laurence B. Ellis, Lewis Dexter, Robert E. Farrand, and James F. Dickson, III, Boston, Massachusetts.
10. RESULTS OF THE SURGICAL TREATMENT FOR MITRAL STENOSIS (ANALYSIS OF 100 CONSECUTIVE CASES).
    O. Henry Janton, Robert P. Glover, and Thomas J. O'Neill, Philadelphia, Pennsylvania.
11. PHYSIOLOGICAL EVALUATION OF PATIENTS WITH MITRAL STENOSIS BEFORE AND AFTER MITRAL VALVULOPLASTY.
    L. Dexter, R. Gorlin, B. M. Lewis, R. J. Spiegl, and F. W. Haynes, Boston, Massachusetts.

12:00 P.M., Friday, June 8

ANNUAL BUSINESS MEETING OF MEMBERS

SECOND SESSION
1:30 P.M., Friday, June 8

Chairman: A. C. Corcoran, Section on Circulation

12. THE DIFFERENTIAL DIAGNOSIS OF PHEOCHROMOCYTOMA.
    Walter F. Kvale and Grace M. Roth, Rochester, Minnesota.
13. EFFECTS OF 1-HYDRAZINO-PHTHALAZINE IN NEUROGENIC HYPERTENSION.
    Henry A. Schroeder, Saint Louis, Missouri.
14. COMPARISON OF THE PHYSIOLOGICAL DISPOSITION OF TROMEXAN AND DICUMAROL IN MAN.
    Bernard B. Brodie, Murray Weiner, George Simson, John Burns, Shepard Shapiro, and J. Murray Steele, New York, New York.
15. THE CAUSES OF SYMPATHECTOMY FAILURE.
    Milton Mendlowitz and Arthur S. W. Touroff, New York, New York.
16. THE INFLUENCE OF LOCAL HEAT AND COLD ON SKIN OXYGEN TENSION IN NORMAL AND ISCHEMIC EXTREMITIES AS DETERMINED BY THE POLAROGRAPHIC METHOD.
    Orville Horwitz and Hugh Montgomery, Philadelphia, Pennsylvania.
17. SURGICAL TREATMENT OF LYMPHEDEMA.
    Gerald H. Pratt, New York, New York.
18. TREATMENT OF MASSIVE EDEMA WITH NITROGEN MUSTARD.
    Robert D. Taylor, A. C. Corcoran, and Irvine H. Page, Cleveland, Ohio.
19. POTASSIUM DEFICIENT DIET AND EFFECT ON BLOOD PRESSURE OF RATS.
    Meyer Friedman, S. Charles Freed, and Ray Rosenman, San Francisco, California.
20. **GEORGE E. BROWN MEMORIAL LECTURE**—PATHOGENESIS AND TREATMENT OF THROMBOSIS.
    Irving S. Wright, New York, New York.

THIRD SESSION
9:00 A.M., Saturday, June 9

Chairman: Howard B. Sprague, President, American Heart Association

21. ABNORMAL BALLISTIC COMPLEXES: THEIR RELATIONSHIPS TO OTHER EVENTS OF THE CIRCULATORY DYNAMICS.
    P. T. Kuo, Truman G. Schnabel, Jr., and Calvin F. Kay, Philadelphia, Pennsylvania.

22. CLINICAL BALLISTOCARDIOGRAPHY: A NEW AID IN CARDIAC DIAGNOSIS.
Kenneth Chesky, Leon Pordy, Marvin Moser, Robert Taymor, and Arthur M. Master, New York, New York.
23. THE SPATIAL DISTRIBUTION OF BODY MOVEMENTS DUE TO CARDIOVASCULAR FORCES: VECTOR BALLISTOCARDIOGRAPHY.
William R. Scarborough, B. M. Baker, Jr., J. Beser, R. E. Mason, and M. L. Singewald, Baltimore, Maryland.
24. STUDIES ON THE VALIDITY AND APPLICATIONS OF THE SPATIAL VECTOCARDIOGRAM.
W. R. Milnor, A. Genecin, S. A. Talbot, and E. V. Newman, Baltimore, Maryland.
25. SPATIAL VECTOCARDIOGRAPHY: ITS TECHNIQUE BASED ON A CUBE ARRANGEMENT OF ELECTRODE PLACEMENT AND ITS CLINICAL IMPORTANCE.
Arthur Grishman, Leonard Scherlis, and Richard P. Lasser, New York, New York.
26. AREA DISPLAYS OF THE ELECTRICAL ACTIVITY OF THE HEART.
Stanford Goldman, W. F. Santelmann, Jr., Conger Williams, and Fred Alexander, Boston, Mass.
27. STUDIES OF THE EXTENT OF VENTRICULAR EMPTYING UNDER VARIOUS CONDITIONS USING LOW FREQUENCY CARDIAC VIBRATIONS.
John Foulger, Wilmington, Delaware.
28. TEACHING HEART SOUNDS, MURMURS, AND ARRHYTHMIAS BY TAPE RECORDINGS.
George David Geckeler and Daniel Mason, Philadelphia, Pennsylvania.
29. **LEWIS A. CONNER LECTURE**—THE HEART AND THE THYROID WITH PARTICULAR REFERENCE TO I_{131} TREATMENT OF HEART DISEASE.
Herrman L. Blumgart, Boston, Massachusetts.

FOURTH SESSION
1:30 P.M., Saturday, June 9

Chairman: E. Cowles Andrus, Chairman, Program Committee

30. THE DETERMINATION OF THE RESIDUAL VOLUME OF BLOOD IN THE RIGHT VENTRICLE OF NORMAL AND DISEASED HUMAN HEARTS.
D. Carroll, W. Falholt, R. Heimbecker, G. Mudd, C. Ferencz, and R. J. Bing, Baltimore, Md.
31. DIAGNOSTIC APPLICATIONS OF CONTINUOUSLY RECORDED EVANS BLUE DILUTION CURVES IN ARTERIAL BLOOD.
John W. Nicholson, III, Howard B. Burchell, and Earl H. Wood, Rochester, Minnesota.
32. THE RELATIONSHIP OF THE CARDIOVASCULAR AND RENAL EFFECTS OF INTRAVENOUS DIGOXIN IN CONGESTIVE HEART FAILURE.
L. W. Eichna, S. J. Farber, A. R. Berger, D. P. Earle, B. Rader, E. Pellegrino, R. E. Albert, J. D. Alexander, H. Taube, and S. Youngwirth, New York, New York.
33. BILATERAL TOTAL ADRENALECTOMY FOR HYPERTENSIVE VASCULAR DISEASE.
John P. Merrill, George W. Thorn, and J. Hartwell Harrison, Boston, Massachusetts.
34. THE USE OF DEXTRAN IN THE TREATMENT OF SHOCK.
Joseph S. Wilson, Walter L. Bloom, Joseph T. Doyle, and James V. Warren, Atlanta, Georgia.
35. THE USE OF A COMBINATION OF ANION AND CATION EXCHANGE RESINS IN THE TREATMENT OF EDEMA AND ASCITES.
B. L. Martz, K. G. Kohlstaedt, and O. M. Helmer, Indianapolis, Indiana.
36. RESIN THERAPY IN CHRONIC CONGESTIVE HEART FAILURE.
Carl Voyles, Jr. and Edward S. Orgain, Durham, North Carolina.
37. CORRECTION OF THE CONGESTIVE FAILURE SYNDROME IN HEART DISEASE WITHOUT THE USE OF DIGITALIS.
R. R. Schemm and W. W. Hurst, Great Falls, Montana.
38. HYPERSENSITIVITY TO MERCUHYDRIN.
John F. Whitman and William L. Proudfit, Cleveland, Ohio.
39. THE CORONARY CIRCULATION IN PATIENTS WITH SEVERE EMPHYSEMA, COR PULMONALE, AND SEVERE ANEMIA.
Henry A. Zimmerman and Arthur F. Young, Cleveland, Ohio.
40. ELECTROLYTE BALANCE FOLLOWING HUMAN MYOCARDIAL INFARCTION: EVIDENCE OF A PROBABLE STRESS REACTION.
John J. Sampson, Kalmen A. Klinghoffer, Robert B. Kalmanson, Paul Toch, and Meyer Friedman, San Francisco, California.

TO BE READ AT ANY SESSION IF TIME PERMITS

41. THE ABNORMAL SERUM LIPID PATTERN IN PATIENTS WITH CORONARY ARTERIOSCLEROSIS.
Alfred Steiner, Forrest E. Kendall, and James L. Mather, New York, New York.
42. ELECTROCARDIOGRAPHIC STUDIES DURING CARDIAC SURGERY.
Edward J. Jaruszewski, Herman K. Hellerstein, and Harold Feil, Cleveland, Ohio.
43. EXPERIMENTAL PRODUCTION AND NATURE OF AURICULAR TACHYCARDIA IN MAN.
Eliot Corday, Robert Oblath, and Alfred Goldman, Los Angeles, California.
44. PRIMARY PULMONARY HYPERTENSION IN CHILDREN.
Herbert E. Griswold, Jr., James H. Lium, George A. Nash, Donald M. Pitcairn, William S. Conklin, Walter A. Gross, Jr., and Donald W. Rennie, Portland, Oregon.
45. THE EFFECT OF BREATHING 100% OXYGEN ON THE PULMONARY ARTERIAL PRESSURE IN MAN.
Sidney H. Dressler, Abe Ravin, N. Balfour Slonim, and Oscar J. Balchum, Denver, Colorado.
46. OBSERVATIONS ON ALTERATIONS IN CARDIOVASCULAR DYNAMICS RESULTING FROM SUGICAL PROCEDURES ON THE HEART AND GREAT VESSELS IN MAN.
Hugh F. Fitzpatrick, Ralph A. Deterling, Jr., Arthur H. Blakemore, and George H. Humphreys, II, New York, New York.

7:30 P.M., Saturday, June 9
ANNUAL DINNER

NOTES

NOTES